BLA: ***99-1488***
PEG-INTRON (Peginterferon alfa-2b) for the treatment of Hepatitis C.
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Schering Corporation

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Summary

This reviewer has analyzed the clinical trial data and examined the results of the statistical analyses included in this BLA submission. The results of CBER's analyses are consistent with those provided in the submission. Only some of the important results related to the primary endpoint are produced in this report.

The efficacy results from this pivotal study show that the combined virologic and ALT response rates in PEG-Intron, 1.0 µg/kg (23.5%) and PEG-Intron, 1.5 µg/kg (22.7%) are significantly superior to that in Interferon alfa-2b, 3 MIU (12.1%). The observed P-values for PEG-Intron 1.0 µg/kg vs. Interferon alfa-2b 3 MIU and PEG-Intron 1.0 µg/kg vs. Interferon alfa-2b, 3 MIU were 0.0002 and 0.0005, respectively. The response rate in PEG-Intron, 0.5 µg/kg arm (16.5%) was not significantly different from the control arm (P=0.113).

Study Design

The pivotal trial in this application was a randomized, active controlled, multicenter, double blind (with respect to PEG-Intron dose) study to evaluate the safety and efficacy of PEG-Intron in the treatment of chronic hepatitis C. A total of 1224 eligible patients were randomized to interferon alfa-2b and PEG-Intron as follows:

- PEG-Intron, 0.5 μg/kg SC (QW): 315 patients
- PEG-Intron, 1.0 μg/kg SC (QW): 298 patients
- PEG-Intron, 1.5 μg/kg SC (QW): 304 patients
- Interferon alfa-2b, 3 MIU SC TIW: 307 patient

A total of 5 randomized patients were not treated in this trial: one (patient #0941) in PEG-Intron, 1.0 μg/kg SC (QW) arm and four (#0754, #0903, #0302, and #0427) in Interferon alfa-2b, 3 MIU SC TIW arm. These patients are included in the analysis.

Interferon alfa-2b (control arm) is an approved product for the treatment of chronic hepatitis C. Treatment was administered for 48 weeks and the patients were followed for an additional 24 weeks. The primary efficacy endpoint for our evaluation was a composite of ALT normalization and loss of detectable serum HCV-RNA/qPCR at the end of follow-up (i.e., at the end of 72 weeks). The secondary endpoints included in the protocol were improvement in Knodell HAI liver biopsy scores (I+II+III) defined as a decrease in the posttreatment score ≥ 2 units relative to pretreatment, time to response, time to relapse, and association of sustained response rates with baseline demographic and disease characteristics.

From CBER's perspectives, the primary endpoint for this study (and other clinical trials of interferon and hepatitis C) was the loss of detectable serum HCV-RNA/qPCR and normalization of ALT at the end of follow-up (NOT at the end of treatment or any other time prior to the end of follow-up). The protocol specified primary treatment comparison was interferon alfa-2b vs. the highest dose of PEG-Intron (1.5 μg/kg). However, it should be noted that there are three PEG-Intron arms in this study and the issue of the primary treatment comparison was an unresolved item in this protocol. The resulting multiplicity with respect to the primary endpoint comparisons would have some effect on the P-values. Nevertheless, the data show highly significant differences (with very small P-values) between Intron and the two higher doses of PEG-Intron arms. Thus, any adjustment for multiple comparisons would have negligible effect of the observed P-values.

All primary endpoint comparisons were done using the Chi-Square test.

Results

1. Virologic Response

The virologic response rates in three PEG-Intron arms and the control group at the end of treatment and at the end of follow-up are given in Table 1. This table also provides the observed difference between the PEG-Intron and the control, the 95% Confidence Interval around this difference, and the P-values for the comparison between the PEG-Intron and the control groups.

At the end of follow-up, the response rates in all three PEG-Intron groups are significantly greater than the response rate in the control group. The difference between 1.5 μg/kg PEG-Intron and the control (the protocol specified primary comparison) is 11.3% (95% CI: 5.3, 17.3; P=0.0003). These data do not provide clear evidence of a dose-response relationship.

2. Combined ALT and Virologic Response

The combined ALT and virologic response rates are given in Table 2. These results are very similar to the virologic response rates given in Table 1. Again, the protocol specified primary comparison (1.5 μg/kg PEG-Intron vs. control) shows an improvement of 10.7% (95% CI: 4.7, 16.6; P=0.0005). It is interesting to note that the difference between 0.5 μg/kg PEG-Intron and the control group is not significant (P=0.113).

3. Baseline HCV Genotype and Virologic Response

HCV genotypes are known predictors of viral response to alfa interferon treatment. An analysis of the viral response by patient's HCV genotype is given in Table 3. The response rate in patients with Genotype 1 is lower than those in patients with non-Genotype 1. However, the intermediate and high doses of the PEG-Intron arms are significantly better than the control arm in both genotypes.

4. Sustained Virologic Response by Time to First Negative HCV-RNA

Early virologic response is another predictor of sustained virologic response with interferon treatment in hepatitis C. The data in Table 4 show that 77-86% (all four groups) of the patients who were HCV-RNA negative at Week 4 became sustained virologic responders (i.e.,

responders at the end of follow-up). Almost all of the remaining sustained responders were HCV-RNA negative by Week 24 (Table 4).

5. Time to Relapse

Relapse was defined in the protocol as undetectable HCV-RNA (<100 copies/ml of serum) at the end of treatment followed by a positive HCV-RNA level at Follow-up Week 24. The data in Table 5 show that the majority of the relapsed subjects returned to HCV-RNA positive status by Follow-Up Week 4.

Comments

1. The results of this trial show that, in comparison with Interferon alfa-2b 3 MIU, 1.0 μg/kg PEG-Intron and 1.5 μg/kg PEG-Intron produces significantly improved virologic and combined ALT and virologic response rates. The combined ALT and virologic response rates in 1.0 μg/kg PEG-Intron and 1.5 μg/kg PEG-Intron are very similar (11.4% vs. 10.7%).

2. These improvements are seen in both Genotype 1 and non-Genotype 1 patients. However, the response rates in non-Genotype 1 patients are higher that those in Genotype 1 patients.

3. Almost all of the sustained responders became HCV-RNA negative by the Treatment Week 24.

4. The majority of the relapsed subjects returned to HCV-RNA positive status by Follow-Up Week 4.

Table 1. Virologic Response (<100 copies/ml).

Outcome	**A** PEG-Intron 0.5 µg/kg (N=315)	**B** PEG-Intron 1.0 µg/kg (N=298)	**C** PEG-Intron 1.5 µg/kg (N=304)	**D** Interferon alfa-2b 3 MIU (N=307)	% Difference **A – D** (95% CI)	% Difference **B – D** (95% CI)	% Difference **C – D** (95% CI)
End of Tx	105 (33.3)	121 (40.6)	149(49.0)	73 (23.8)	9.6 (2.5, 16.6) P=0.008	16.8 (9.5, 24.2) P<0.0001	5.2 (17.9, 32.6) P<0.0001
End of Follow-up	57 (18.1)	73 (24.5)	71 (23.4)	37 (12.1)	6.0 (0.4, 11.6) P=0.035	12.4 (6.4, 18.5) P=0.0001	11.3 (5.3, 17.3) P=0.0003

Table 2. Combined ALT (normal) and Virologic Response (<100 copies/ml).

Outcome	**A** PEG-Intron 0.5 µg/kg (N=315)	**B** PEG-Intron 1.0 µg/kg (N=298)	**C** PEG-Intron 1.5 µg/kg (N=304)	**D** Interferon alfa-2b 3 MIU (N=307)	% Difference **A – D** (95% CI)	% Difference **B – D** (95% CI)	% Difference **C – D** (95% CI)
End of Tx	79 (25.1)	92 (30.9)	100 (32.9)	61 (19.9)	5.2 (-1.3, 11.8) P=0.120	11.0 (4.1, 17.9) P=0.002	13.0 (6.1, 19.9) P=0.0003
End of Follow-up	52 (16.5)	70 (23.5)	69 (22.7)	37 (12.1)	4.5 (-1.0, 9.9) P=0.113	11.4 (5.4, 17.5) P=0.0002	10.7 (4.7, 16.6) P=0.0005

Table 3. Baseline HCV Genotype and Virologic Response (<100 copies/ml).

Outcome	**A** PEG-Intron 0.5 µg/kg (N=315)	**B** PEG-Intron 1.0 µg/kg (N=298)	**C** PEG-Intron 1.5 µg/kg (N=304)	**D** Interferon alfa-2b 3 MIU (N=307)	% Difference **A – D** (95% CI)	% Difference **B – D** (95% CI)	% Difference **C – D** (95% CI)
End of Tx							
Genotype 1	52/211 (24.6)	50/199 (25.1)	87/223 (39.0)	32/217 (14.8)	9.9 (2.4, 17.4) P=0.010	10.4 (2.7, 18.0) P=0.008	24.3 (16.3, 32.2) P<0.0001
Genotypes 2/3/4/5/6	50/98 (51.0)	69/96 (71.9)	60/78 (76.9)	41/85 (48.2)	2.8 (-11.7,17.3) P=0.707	23.6 (9.7, 37.6) P=0.001	28.7 (14.5,42.8) P=0.0002
End of Follow-up							
Genotype 1	22/211 (10.4)	28/199 (14.1)	31/223 (13.9)	14/217 (6.5)	4.0 (-1.3, 9.2) P=0.139	7.6 (1.8, 13.5) P=0.010	7.5 (1.9, 13.0) P=0.010
Genotypes 2/3/4/5/6	33/98 (33.7)	43/96 (44.8)	39/78 (50.0)	23/85 (27.1)	6.6 (-6.7, 19.9) P=0.333	17.7 (4.0, 31.5) P=0.013	22.9 (8.4, 37.5) P=0.003

Table 4. Sustained Virologic Response by Time to First Negative HCV-RNA/qPCR.

Time of First Negative HCV-RNA Response (weeks)	PEG-Intron 0.5 µg/kg (N=57)	PEG-Intron 1.0 µg/kg (N=73)	PEG-Intron 1.5 µg/kg (N=71)	PEG-Intron 3 MIU (N=37)
4	26/32 (81.3)	33/39 (84.6)	46/60 (76.7)	18/21 (85.7)
12	20/42 (47.6)	31/60 (51.7)	19/60 (31.7)	15/41 (36.6)
24	7/35 (20.0)	4/31 (12.9)	5/33 (15.2)	4/23 (17.4)
36	1/10 (10.0)	1/8 (12.5)	0/15 (0.0)	0/4 (0.0)
48	2/7 (28.6)	2/5 (40.0)	0/5 (0.0)	0/4 (0.0)
End of Tx	1/1 (100.0)	2/4 (50.0)	0/1 (0.0)	0/0 (0.0)

Table 5. Time to Relapse.

Follow-Up Time (weeks)	PEG-Intron 0.5 µg/kg (N=105)	PEG-Intron 1.0 µg/kg (N=121)	PEG-Intron 1.5 µg/kg (N=149)	PEG-Intron 3 MIU (N=73)
4	37 (35.2)	44 (36.4)	65 (43.6)	31 (42.5)
12	8 (7.6)	1 (0.8)	6 (4.0)	3 (4.1)
24	3 (2.9)	4 (3.3)	4 (2.7)	1 (1.4)

N is the number of patients who were HCV-RNA/QPCR negative at the end of treatment.